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InterAct Consortium; LifeLines Cohort Study Grp

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Multi-ancestry genome-wide association study of lipid levels incorporating gene-alcohol interactions

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Running head: Gene-alcohol interactions and lipid levels

Abbreviations: low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), degrees of freedom (DF), genome-wide association study (GWAS), false discovery rate (FDR).

ABSTRACT

An individual's lipid profile is influenced by genetic variants and alcohol consumption, but the contribution of interactions between these exposures has not been studied. We therefore incorporated gene-alcohol interactions into a multi-ancestry genome-wide association study of levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. We included 45 studies in Stage 1 (genome-wide discovery) and 66 studies in Stage 2 (focused follow-up), for a total of 394,584 individuals from five ancestry groups. Genetic main and interaction effects were jointly assessed by a 2 degrees of freedom (DF) test, and a 1 DF test was used to assess the interaction effects alone. Variants at 495 loci were at least suggestively associated ($P < 1 \times 10^{-6}$) with lipid levels in Stage 1 and were evaluated in Stage 2, followed by combined analyses of Stage 1 and Stage 2. In the combined analysis of Stage 1 and Stage 2, 147 independent loci were associated with lipid levels at $P < 5 \times 10^{-8}$ using 2 DF tests, of which 18 were novel. No genome-wide significant associations were found testing the interaction effect alone. The novel loci included several genes (*PCSK5*, *VEGFB*, and *AICF*) with a putative role in lipid metabolism based on existing evidence from cellular and experimental models.

Keywords: Alcohol consumption, gene-environment interactions, gene-lifestyle interactions, genome-wide association study, lipid levels, cholesterol, triglycerides

Serum concentrations of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) are modifiable risk factors for cardiovascular disease, the leading cause of death globally (1). Lipid levels are influenced by multiple exposures, including genetic and lifestyle factors. The genetic factors influencing lipid levels have been widely studied (2-8), and large-scale genome-wide association studies (GWAS) have identified 236 loci associated with HDL-C, LDL-C, and TG, which account for up to ~12 percent of the total trait variance in the studied populations (5, 7).

Lifestyle factors, such as alcohol consumption, also associate considerably with lipid levels: in epidemiologic studies, higher alcohol consumption is associated with improved lipid profile, including associations with HDL-C levels, HDL particle concentration, and HDL-C subfractions (9, 10). The relationship between alcohol use and LDL-C or TG is less clear, with some studies reporting positive while others reported negative associations (11-20). A causal role of low-to-moderate alcohol consumption in improving overall lipid profile is supported by intervention studies (19), and more recently by Mendelian randomization studies (21, 22).

Potential modification of genetic effects on lipid levels by lifestyle exposures, including alcohol consumption, is relatively unexplored (23). Genetic association studies accounting for potential gene-alcohol interactions may lead to the identification of novel lipid loci and may reveal new biological insights that can potentially be explored for treatment or prevention of dyslipidemia.

In order to investigate the potential modulating role of alcohol consumption in the genetic architecture of lipid levels, and identify novel HDL-C, LDL-C, and TG loci, we performed genome-wide gene-alcohol interaction meta-analyses of LDL-C, HDL-C and TG.

METHODS

Overall design

Table 1 shows the overall design of this study, conducted within the setting of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium Gene-Lifestyle Interactions Working Group (24, 25). In order to decrease the computational burden we carried out genome-wide analyses in Stage 1, and followed up suggestively associated variants in Stage 2, with the combined analysis of Stage 1 and Stage 2 serving as the primary analysis (26). We used two complementary approaches to model interactions: 1) a 2 degrees of freedom (DF) test was used to jointly assess both the genetic main effect and interaction effect on lipid levels, and 2) a 1 DF test was used to assess the effect of interactions alone. The 2 DF test is more powerful when there is both a genetic main and interaction effect, and it may thus help identify interaction effects for which the 1 DF test is underpowered (27).

Overview of participating studies

This study includes men and women between the ages of 18-80 from five ancestry groups: European, African, Asian, Hispanic, and Brazilian. Each study obtained informed consent from participants and approval from the appropriate institutional review boards. Although the participating studies are based on different study designs and populations, all of them have data on lipid levels, alcohol consumption, and genotypes across the genome.

In total, this study comprises 394,584 individuals. Stage 1 included 89,893 European, 20,989 African, 12,450 Asian, and 3,994 Hispanic ancestry participants for an overall total of 127,326 individuals from 45 studies (Web Table 1), namely: Age Gene/Environment Susceptibility Reykjavik Study (AGES: 1967 - Reykjavik, Iceland), Atherosclerosis Risk in Communities study (ARIC: 1987-1989 - Washington County, MD; Forsyth County, NC; Jackson, MS; and

Minneapolis, MN), Coronary Artery Risk Development in Young Adults (CARDIA: 1985-1986
 - Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA), Cardiovascular Health
 Study (CHS: 1989-1990 and 1992-1993 - Forsyth County, NC; Sacramento County, CA;
 Washington County, MD and Pittsburgh, PA), CROATIA-Korcula (2007 - Korcula, Croatia),
 CROATIA-Vis (2003-2004 - Vis, Croatia), Erasmus Rucphen Family study (ERF: 2002-2005 -
 Rotterdam, the Netherlands), FamHS (FamHS: 1992-1995 - Salt Lake City, UT; Forsyth County,
 NC; Minneapolis, MN; and Framingham, MA), Framingham Heart Study (Framingham: 1948 -
 Framingham, MA), Genetic Epidemiology Network of Arteriopathy (GENOA: 1995-2000 -
 Rochester, MN and Jackson, MS), Genetic Epidemiology Network of Salt Sensitivity (GenSalt:
 2003-2005 - Hebei; Henan; Shandong; Shaanxi; and Jiangsu, China), Generation Scotland:
 Scottish Family Health Study (GS:SFHS: 2006-2011 - Scotland), Health, Aging and Body
 Composition *Study* (HABC: 1997-1998 - Pittsburgh, PA and Memphis, TN), Healthy Aging in
 Neighborhoods of Diversity across the Life Span (HANDLS: 2004-2009 - Baltimore, MD),
 Health, Risk Factors, Exercise Training and Genetics (HERITAGE: 1995-2000 - AZ; IN; MN;
 TX; and Quebec, Canada), Howard University Family Study (HUFS: 2001-2008 - Washington,
 DC), Hypertension Genetic Epidemiology Network (HyperGEN: 1996-1999 - Birmingham, AL;
 Salt Lake City, UT; Forsyth County, NC; Minneapolis, MN; and Framingham, MA), Jackson
 Heart Study (JHS: 2000-2004 - Jackson, MS), Multi-Ethnic Study of Atherosclerosis (MESA:
 2000-2002 - Los Angeles, CA; St. Paul, MN; Chicago, IL; Winston-Salem, NC; Baltimore, MD
 and New York, NY), Netherlands Epidemiology of Obesity study (NEO: 2008-2012 - Leiden,
 the Netherlands), Rotterdam Study 1 (RS1: 1990 - Rotterdam, the Netherlands), Rotterdam
 Study 2 (RS2: 2000-2001 - Rotterdam, the Netherlands), Rotterdam Study 3 (RS3: 2006-2008 -
 Rotterdam, the Netherlands), Singapore Chinese Eye Study (SCES: 2009-2011 - Singapore),

Singapore Chinese Health Study (SCHS: 1993-1998 - Singapore), Singapore Malay Eye Study (SiMES: 2004-2006 - Singapore), Singapore Indian Eye Study (SINDI: 2007-2009 - Singapore), Singapore 2 (SP2-1M: 1982-1998 - Singapore), Women's Genome Health Study (WGHS: 1992-1995 - USA), and Women's Health Initiative (WHI: 1993-1998 - USA).

Stage 2 included 136,986 European, 4,475 African, 108,431 Asian, 13,714 Hispanic, and 3,652 Brazilian ancestry individuals for an overall total of 267,258 individuals from the following studies (**Web Table 2**): 1982 Pelotas Birth Cohort Study (1982 - Pelotas, Brazil), African American Diabetes Heart Study (AA-DHS: 1998-2005 - Winston-Salem, NC), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT: 1998-2000 - Denmark; Finland; Ireland; Norway; Sweden; UK), Baependi Heart Study (2010 - Baependi, Brazil), BBJ (2003-2008 - Japan), Beijing Eye Study (2001 - Beijing, China), British Genetics of Hypertension (BRIGHT: 1995 - UK), Cardio-metabolic Genome Epidemiology Network, Amagasaki Study (CAGE-Amagasaki: 2002-2003 - Amagasaki, Japan), Data from an Epidemiological Study on the Insulin Resistance (DESIR-1: 1994-1996 - France), Dongfeng-Tongji Cohort Study (DF-TJ: 2008 - Shiyang city, China), Diabetes Heart Study (DHS: 1998-2005 - Winston-Salem, NC), Dose Responses to Exercise Training (DR's EXTRA: 2005-2006 - Kuopio, Finland), Estonian Genome Center - University of Tartu (EGCUT: 2002-2010 - Estonia), European Prospective Investigation into Cancer and Nutrition (EPIC: 1992-1997 - France; Italy; Spain; UK; the Netherlands; Germany; Sweden; Denmark; Norway; and Greece), Fenland Study (FENLAND-GWAS: 1950-1975 - Cambridgeshire, England), Finland-United States Investigation of NIDDM Genetics (FUSION: 1994 - Finland), Genetic Studies of Atherosclerosis Risk (GeneSTAR: 1983-2006 - Baltimore, MD), Gene x Lifestyle Interactions and Complex Traits Involved in Elevated Disease Risk (GLACIER: 1985-2004 - Sweden), Genetic Regulation of Arterial Pressure of Humans in

the Community (GRAPHIC: 2003-2005 - Leicestershire, UK), Hispanic Community Health Study/ Study of Latinos (HCHS/SOL: 2008-2011 - Chicago, IL; Miami, FL; New York City, NY; and San Diego, CA), Health & Retirement Study (HRS: 2006-2010 - USA), Hypertension Genetic Epidemiology Network (HyperGEN-AXIOM: 1996-1999 - Birmingham, AL; Salt Lake City, UT; Forsyth County, NC; Minneapolis, MN; and Framingham, MA), Italian Network Genetic Isolates - Carlantino (INGI-CARL: 2005-2006 - Carlantino, Italy), Italian Network Genetic Isolates - Friuli-Venezia Giulia (INGI-FVG: 2013 - Friuli-Venezia Giulia, Italy), EPIC-InterAct Case-Cohort Study (InterAct: 1991-2007 - France; Italy; Spain; UK; the Netherlands; Germany; Sweden; and Denmark), Insulin Resistance Atherosclerosis Study (IRASC and IRASFS: 1999-2005 - San Antonio, TX; San Luis Valley, CO), Cooperative Health Research in the Augsburg Region S3 (KORA_S3: 1994-1995 - Augsburg, Germany), Cooperative Health Research in the Augsburg Region S4 (KORA_S4: 1991-2001 - Augsburg, Germany), Lothian Birth Cohort 1936 (LBC1936: 2004-2007 - Lothian, Scotland), LifeLines (2006-2013 - the Netherlands), London Life Sciences Prospective Population study (LOLIPOP: 2003-2007 - London, England), Long Life Family Study (LLFS: 2006-2009 - Boston, MA; New York City, NY; Pittsburgh PA; and Denmark), Kingston Gene-by-environment (Loyola GxE: 1994-1995 - Kingston, Jamaica), Spanish Town (Loyola SPT: 1994-1995 - Kingston, Jamaica), Metabolic Syndrome In Men (METSIM: 2005-2010 - Kuopio, Finland), Netherlands Study of Depression and Anxiety (NESDA: 2004-2007 - the Netherlands), French obese cases (OBA: 2005 - France), Prevention of RENal and Vascular ENd stage Disease study (PREVEND: 1997-1998 - Groningen, Netherlands), Precocious Coronary Artery Disease (PROCARDIS: 2004-2008 - UK; Italy; Sweden; and Germany), Ragama Health Study (RHS: 2007 - Ragama, Sri Lanka), Stockholm Heart Epidemiology Program (SHEEP: 1992-1994 - Stockholm county, Sweden),

Study of Health in Pomerania (SHIP-0: 1997-2001 - Greifswald, Stralsund and Anklam Germany), Study of Health in Pomerania - Trend (SHIP-Trend: 2008-2012 - Greifswald, Stralsund and Anklam Germany), Shanghai Women's Health Study/ Shanghai Men's Health Study (SWHS/SMHS: 1997-2000 - Shanghai, China), TwinGene of the Swedish Twin Registry (TWINGENE: 2004-2008 - Sweden), and Cardiovascular Risk in Young Finns Study (YFS: 1980 - Finland).

Phenotype and lifestyle variables

Three lipids traits were analyzed separately: HDL-C (mg/dL), LDL-C (mg/dL), and TG (mg/dL). HDL-C and TG were directly assayed, while LDL-C was either directly assayed or estimated using the Friedewald equation: $LDL-C = TC - HDL-C - (TG / 5)$ (28). Only fasting samples (≥ 8 hours) were used to assay TG, and the Friedewald equation was only used in samples with fasting $TG \leq 400$ mg/dL. LDL-C values were adjusted for use of statins (**Web Appendix**). HDL-C and TG were natural log transformed prior to analyses.

Alcohol consumption was assessed using two dichotomized alcohol consumption variables: 'current drinking' status, defined as any recurrent drinking behavior, and 'regular drinking' status, as the subset of current drinkers who consume at least two drinks per week. Because the standard pure ethanol content in one alcoholic drink may vary among countries, for this study a standard drink was defined to contain approximately 13g of pure ethanol, and this measure was used to standardize the definitions across studies.

Genotyping and imputation

Information on genotyping and imputation for each of the Stage 1 and Stage 2 studies are presented in **Web Table 3** and **Web Table 4**, respectively. For imputation, most studies used the

1000 Genomes Project Phase I Integrated Release Version 3 Haplotypes (2010-11 data freeze, 2012-03-14 haplotypes), which contain haplotypes for 1,092 individuals from multiple ancestry groups (29).

Study-specific analysis

Study-specific regression analyses were performed for each variant, using models containing the genetic variant, alcohol consumption variable (current drinking or regular drinking status), and their interaction. Variants were coded according to the additive model, so that the beta coefficient represents the effect size per copy of the coded allele. These regressions were adjusted for age, sex, ancestry-informative principal components, and study-specific variables where appropriate (such as center for multi-center studies). Information on principal components and study-specific variables adjusted for in each study-specific analysis is provided in **Web Tables 3-4**.

Each study in Stage 1 performed genome-wide association analyses within each ancestry and provided the estimated genetic main effect, estimated interaction effect and a robust estimate of the corresponding covariance matrix. Each study in Stage 2 performed analyses only for the selected variants identified in Stage 1. Study-specific association analyses were performed using various software (**Web Appendix** and **Web Tables 3-4**). Extensive quality control using the R package EasyQC was performed for all study-specific GWAS results, as described in the **Web Appendix** (30).

Meta-analysis

We implemented METAL to meta-analyze the genetic main and interaction effects jointly using the 2 DF approach by Manning *et al.* (27, 31), and to meta-analyze the interaction coefficients

alone using inverse-variance weighted meta-analysis (1 DF test). For each meta-analysis, results were obtained from Wald tests, calculated using genetic main effect estimates, interaction effect estimates, and robust estimates of the corresponding covariance matrix.

In Stage 1 ancestry-specific meta-analyses were performed for each of the 12 analyses (3 lipids \times 2 alcohol consumption exposures \times 2 tests). Genomic control correction was applied twice (32), first to the study-specific GWAS results (**Web Table 5**), and then to the ancestry-specific meta-analysis results. The results from each ancestry group were then combined in a trans-ancestry meta-analysis.

The variants that were at least suggestively associated ($P\text{-value} < 1 \times 10^{-6}$) in any of Stage 1 interaction analyses were pursued for Stage 2 analysis. In Stage 2, we used the same approaches as in Stage 1 to perform ancestry-specific and trans-ancestry meta-analyses. Finally, ancestry-specific and trans-ancestry meta-analyses were performed to combine Stage 1 results with Stage 2 results. Variants with $P\text{-value} < 5 \times 10^{-8}$ for either the 2 DF joint test of genetic main and interaction effects or the 1 DF test of interaction effects were considered genome-wide significant. False discovery rate (FDR) $q\text{-values}$ were calculated using the Benjamini and Hochberg method implemented in the “p.adjust” function in R, correcting for the number of tests performed in Stage 1. FDR $q\text{-values} < 0.05$ thus indicate a $< 5\%$ false discovery rate even after considering the multiple testing introduced by performing genome-wide analyses on multiple outcomes using multiple models. An independent locus was defined as the ± 1 Mbp region surrounding an index variant. For each locus the closest genes were determined based on proximity to the index variant. For loci with intergenic index variants we provided the closest gene in each direction.

Additional analyses

The percent of variance explained in HDL-C, LDL-C, and TG by all previously known and novel variants was evaluated in ten studies from multiple ancestries (**Web Appendix**).

HaploReg, RegulomeDB, and Genotype-Tissue Expression (GTEx) were used to annotate variants at significant loci (33-35). We also used the Data-driven Expression Prioritized Integration for Complex Traits (DEPICT) software to prioritize genes at the loci associated with lipid levels in the combined analysis of Stage 1 and 2. More details on gene prioritization using DEPICT can be found in the **Web Appendix**.

Lastly, we examined the association of index variants at the 147 significant loci with coronary artery disease and myocardial infarction using publicly available summary association results from a large GWAS of these phenotypes performed by the CARDIoGRAMplusC4D consortium (36).

RESULTS

Descriptive statistics of the studies participating in Stage 1 are shown in **Web Table 1**: 56.1 percent of Stage 1 participants were current drinkers and 39.9 percent were regular drinkers. The Stage 1 genome-wide analyses identified 25,115 variants in 495 independent loci that were at least suggestively associated (P -value $< 1 \times 10^{-6}$) with HDL-C, LDL-C, or TG using either the 1 DF test of the interaction or the 2 DF test that jointly assesses genetic main and interaction effects. The 1 DF interaction test identified 356 suggestively associated variants, while the 2 DF joint test identified an additional 24,759. Manhattan and quantile-quantile plots are shown in **Web Figures 1 and 2, respectively**.

The 25,115 variants were then evaluated in Stage 2. Descriptive statistics of the studies participating in Stage 2 are shown in **Web Table 2**: 58.5 percent of Stage 2 participants were current drinkers and 41.0 percent were regular drinkers. The combined analysis of Stage 1 and Stage 2 identified 22,590 variants at 147 independent loci at genome-wide significance (P -value $< 5 \times 10^{-8}$, **Web Table 6**). All genome-wide significant associations were identified through the 2 DF joint tests of main and interaction effects. There were no genome-wide significant 1 DF interaction associations in the combined analysis of Stage 1 and Stage 2. At genome-wide significance, 95 of the 147 loci were associated with HDL-C, 66 were associated with LDL-C, and 58 were associated with TG. Out of the 147 loci, 60 loci were associated with more than one lipid trait, as shown in a Venn diagram in **Figure 1**.

Novel loci

Of the 147 identified genome-wide significant loci, 18 are novel lipid loci that have not been previously identified by other association studies for HDL-C, LDL-C, TG, or total cholesterol (**Table 2** and **Web Figure 3**) (2-8). A concurrent genetic association study of exonic variants also identified four of these 18 novel loci (37), as indicated in **Table 2**. Eight of the novel loci involved HDL-C, eight involved LDL-C, and seven involved TG, as shown in the heatmap in **Figure 2**. The most significant associations at each of the 18 novel loci all had FDR q -values < 0.05 (**Table 2**), indicating that they are unlikely to be false positives introduced by multiple testing. As shown in forest plots (**Web Figure 4**), the 2 DF associations at the novel loci were predominantly driven by genetic main effects, with a smaller contribution from interaction effects. Furthermore, of the 18 index variants, 15 had at least suggestively significant ($P < 1 \times 10^{-6}$) genetic main effects in Stage 1 (**Web Appendix** and **Web Table 7**). None of the associations at the 18 novel loci displayed heterogeneity across ancestry groups (**Table 2**).

Known loci

The remaining 129 of the 147 significant loci had been identified in previous GWAS of lipid traits (**Web Table 6**) (2-8). This is a subset of all known lipid loci: **Web Table 8** shows the significance of 314 reported index variants in all 236 known lipid loci among all 2 DF joint tests and 1 DF interaction tests of the combined analysis of Stage 1 and Stage 2, or Stage 1 alone for variants not meeting the Stage 2 inclusion criteria (2-8). Considering only the 314 known variants, no 1 DF interactions were significant in the European, African, or trans-ancestry meta-analyses ($P\text{-value} < 8.8 \times 10^{-6}$, corresponding to $0.05 / [314 \text{ variants} \times 3 \text{ lipid traits} \times 2 \text{ alcohol consumption variables} \times 3 \text{ ancestry groups}]$).

Additional analyses

The percentage of variance in LDL-C, HDL-C, and TG explained by various loci was calculated in individual studies from multiple ancestries. Across ancestry groups, the mean variance explained by known lipid loci was 9.1 percent for HDL-C, 10.4 percent for LDL-C, and 7.5 percent for TG. The total percentage of additional variance explained by the 18 novel loci, including both genetic main and interaction effects, was 0.2 for HDL-C, 0.3 for LDL-C, and 0.4 for TG. Ancestry-specific and study-specific estimates are shown in **Web Table 9**.

Functional annotations using HaploReg (33) and RegulomeDB (34) for variants at the 147 loci that were associated in the combined analysis of Stage 1 and 2 are presented in **Web Table 10**, and associations of these variants with gene expression levels from the GTEx database (35) in a variety of tissues are shown in **Web Table 11**. A total of 443 variants were associated with gene expression levels, of which 27 variants were indicated by RegulomeDB as having strong evidence for an effect on enhancer function.

Our gene prioritization analyses with DEPICT highlighted (FDR q -values < 5 percent) 165 genes at HDL-C associated loci, 110 genes at LDL-C associated loci and 87 genes at TG associated loci (**Web Tables 11-14**). Thus, at some loci multiple potential causal genes were prioritized. DEPICT identified 656, 877 and 497 reconstituted gene sets that were significantly enriched (FDR q -values < 5 percent) for genes at HDL-C, LDL-C and TG loci, respectively (**Web Table 15**). This large number of processes and enriched gene sets underscores the complex genetic, biological and physiological mechanisms underlying lipid traits. Among the most significantly enriched gene sets were processes related to “total amount of body fat” and “abnormal liver morphology”. Finally, DEPICT revealed that genes at associated HDL-C, LDL-C or TG loci were significantly enriched (FDR q -values < 5 percent) for association with gene expression in 23 tissues, 14 cell-types and 12 physiological systems (**Web Table 16**). We found a compelling enrichment of genes acting in hepatocytes and liver processes at associated loci for each of the three traits and of genes acting in adipose tissues for HDL-C and TG loci (**Web Table 16, Web Figure 5**).

Fourteen index variants at known lipid loci were associated with coronary artery disease with P -value < 1.7×10^{-4} ($0.05 / [147 \text{ variants} \times 2 \text{ disease outcomes}]$), and eleven of these were also associated with myocardial infarction (**Web Table 17**) (36). None of the index variants at novel loci were significantly associated with these clinical endpoints.

DISCUSSION

We performed a genome-wide association study of lipid levels incorporating interactions with alcohol consumption and identified 147 genome-wide significant lipid loci of which 18 are novel.

Despite the large sample of 394,584 individuals, which is comparable to other successful genetic interaction studies (38, 39), genome-wide significant interactions were not found in the present study. Gene-alcohol interactions also do not appear to have contributed substantially to the discovery of the 18 novel loci, given that the genetic main effect of index variants at 15 of the 18 novel loci passed the Stage 1 suggestive significance threshold. We highlight three of the novel loci below that harbor especially promising candidate genes with putative roles in lipid metabolism based on existing evidence from cellular and experimental models.

One of the newly identified associations for LDL-C maps to Proprotein Convertase Subtilisin/Kexin Type 5 (*PCSK5*), a member of the same gene family as *PCSK9*, which is targeted by new drugs that successfully lower LDL-C levels (40, 41). Several independent lines of evidence support the involvement of *PCSK5* in the regulation of lipid levels. First, a candidate gene study found that variants in *PCSK5* were associated with levels of HDL-C levels (42). Additionally, *in vitro* studies of cell lines show that *PCSK5* inactivates endothelial lipase directly through cleavage, and that it may also inactivate endothelial lipase and lipoprotein lipase indirectly through activation of Angiopoietin-like 3 (43). Endothelial lipase, lipoprotein lipase, and Angiopoietin-like 3 have all been robustly implicated in the regulation of lipid levels, likely with primary roles in the metabolism of HDL-C and triglycerides (3, 44-46). In our study, the *PCSK5* locus was only associated at genome-wide significance with LDL-C levels, and at nominal significance (P -value < 0.05) with TG levels.

One novel locus for TG mapped to the *AICF* gene, which encodes APOBEC1 Complementation Factor. Liu *et al.* also identified the same index variant (rs41274050) in association with TG in a concurrent study (37). They showed that introducing the minor allele of rs41274050 in mice led to increased TG levels, confirming the functional role of this missense variant in the regulation

of TG levels (37). APOBEC1 Complementation Factor forms an enzymatic complex with APOBEC1 and deaminates Apolipoprotein B mRNA (47). This site specific deamination of C to U results in the production of the apoB48 isoform as opposed to the apoB100 isoform (47). The apoB48 isoform is critical in the assembly and secretion of chylomicrons, which mainly carry dietary-derived triglycerides (48). Interestingly, a recent GWAS in individuals of East Asian ancestry identified the *APOBEC1* locus for HDL-C levels (5), an association that we confirmed in our analysis (index variant: 12:7725904:ID). At nominal significance both the index variants near *AICF* and *APOBEC1* were associated with all three lipid traits (P -value < 0.05). Given the role of apoB100 in atherosclerosis, promoting the synthesis of apoB48 instead of apoB100 may represent a possible therapeutic strategy for the prevention of cardiovascular disease (49). Neither the index variant at *AICF* nor *APOBEC1* is significantly associated with coronary artery disease or myocardial infarction in the largest GWAS of these outcomes. However, further studies are needed to characterize their role in cardiovascular disease, given our multi-ancestry design and the European-driven design of the available GWAS data on cardiovascular disease outcomes (**Web Table 17**).

Variants closest to the MACRO Domain Containing 1 (*MACROD1*) gene were associated with HDL-C levels and TG levels. This locus was also reported in the concurrent study by Liu *et al.* (37), although the index variant in their study was located in the Phospholipase C Beta 3 (*PLCB3*) gene, around 120 Kbp away from the index variant in the present study. We found that variants at this locus were associated with expression levels of another nearby gene, Vascular Endothelial Growth Factor B (*VEGFB*), in adipose and heart tissue (**Web Table 11**). VEGF-B is reportedly involved in endothelial fatty acid transport, with *Vegfb*^{-/-} mice showing less accumulation of lipids in muscle, heart, and brown adipose tissue, but a greater uptake of fatty

acids in white adipose tissue, and higher body weight (50). Additionally, inhibition of VEGF-B in a mouse model of type 2 diabetes resulted in improved glycemic profile as well as a reduction of dyslipidemia (51). Mice lacking VEGF-B had lower levels of TG and LDL-C accompanied by higher levels of HDL-C. Subsequent studies on other mouse models did not corroborate these findings: Dijkstra *et al.* found in an independent strain of mice that knocking out VEGF-B had no effect on TG and total cholesterol levels (52), while Rubciuc *et al.* reported that transduction of the human *VEGFB* gene into mice led to increased vascularity in adipose tissue, and improved lipid profile (53, 54). Our results provide insight into the effects of VEGF-B in humans to complement the divergent reports from rodent studies. The A allele of index variant rs190528931 is associated with decreased expression of *VEGFB* in adipose and heart tissue, decreased levels of HDL-C and increased levels of TG. Additionally, rs190528931 was also associated with nominally significant increased levels of LDL-C (P -value < 0.05). Hence, evidence from our study suggests that inhibition of VEGF-B does not improve lipid profile, but instead promotes dyslipidemia.

The strengths of this study include the large sample size and diverse ancestral composition of the sample, and the use of a dense reference panel for genotype imputation (55). A limitation of this study is the imbalance in ancestry groups between Stage 1 and Stage 2. African ancestry individuals were well-represented in Stage 1 but underrepresented in Stage 2. In contrast, Asian and Hispanic ancestry individuals were relatively underrepresented in Stage 1 compared to Stage 2. A more balanced division of participants across Stage 1 and Stage 2 may have led to the identification of additional loci. Additionally, alcohol consumption may be underreported in both self-administered questionnaires and interviews, leading to a loss of statistical power due to misclassification (56). Similarly, the classification of alcohol consumption into categories such

as regular drinkers and current drinkers may have reduced power relative to treating it as a fully quantitative variable (57). Nevertheless, the use of such categories was necessary for harmonizing data from 111 studies with heterogeneous measurement of alcohol consumption. It is plausible that more comprehensive characterization of alcohol consumption could reveal interactions that were missed in our study.

In conclusion, we identified 18 novel loci that were significantly associated with lipid traits, and these include several loci with genes (*PCSK5*, *VEGFB*, and *AICF*) that have a putative role in lipid metabolism based on existing evidence from cellular and experimental models. The associations identified in this study appear to be driven by genetic main effects and it remains uncertain whether alcohol consumption modifies the effect of genetic variants on lipid levels.

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TABLES

Table 1. Layout of the Overall Study Design.

| Stage | No. in Each Ancestry Group | | | | | Meta-Analysis |
|--------------------|----------------------------|---------|---------|----------|-----------|---------------|
| | European | African | Asian | Hispanic | Brazilian | |
| 1 | 89,893 | 20,989 | 12,450 | 3,994 | 0 | 127,326 |
| 2 ^a | 136,986 | 4,475 | 108,431 | 13,714 | 3,652 | 267,258 |
| Total ^b | 226,879 | 25,464 | 120,881 | 17,708 | 3,652 | 394,584 |

For each lipid trait, association analyses were performed, accounting for the two alcohol consumption variables: “current drinker” status and “regular drinker”. For each ancestry group, study-specific results were combined to perform the 1 degree of freedom (DF) test for an interaction effect and the 2 DF joint test of genetic main effect and interaction with drinking exposure. Individuals from five ancestry groups were included: European, African, Asian, Hispanic, and Brazilian. ^aVariants selected for follow-up at $P \leq 1 \times 10^{-6}$ using 1 DF interaction and 2 DF joint tests. ^bVariants significant at $P \leq 5 \times 10^{-8}$ using 2 DF joint or 1 DF interaction test.

Table 2. Novel Loci Discovered in the Combined Analysis of Stages 1 and 2 Using the 2 DF Model that Jointly Tests Main and Interaction Effects.

| rsID | Chr:Position | Alleles ^a | Freq | Closest Gene(s) | Main Effect ^b | Interaction Effect ^b | Joint P-value ^b | Joint FDR q-value ^b | Interaction P-value ^c | Heterogeneity P-value ^d | Most Significant 2 DF Model |
|--------------------------|--------------|----------------------|------|----------------------------|--------------------------|---------------------------------|----------------------------|--------------------------------|----------------------------------|------------------------------------|-----------------------------|
| rs190528931 ^e | 11:63911273 | A/C | 0.04 | <i>MACROD1</i> | 0.0109 | -0.0023 | 1.9×10^{-16} | 3.6×10^{-11} | 0.32 | 0.96 | META - HDL-C - CURDRINK |
| rs7904973 ^e | 10:124693587 | T/G | 0.55 | <i>C10orf88</i> | 0.9200 | -0.1500 | 1.9×10^{-15} | 3.5×10^{-10} | 0.38 | 0.89 | META - LDL-C - CURDRINK |
| rs73729083 | 7:137559799 | C/T | 0.91 | <i>CREB3L2</i> | 4.0100 | 0.6500 | 8.2×10^{-15} | 1.4×10^{-9} | 0.57 | 0.22 | META - LDL-C - CURDRINK |
| rs80080062 | 3:185812169 | G/C | 0.87 | <i>ETV5</i> | 0.0061 | 0.0031 | 1.1×10^{-12} | 1.7×10^{-7} | 0.38 | 0.85 | META - HDL-C - REGDRINK |
| rs7140110 | 13:114544024 | C/T | 0.73 | <i>GAS6-AS1</i> | -0.0100 | -0.0040 | 3.4×10^{-12} | 5.1×10^{-7} | 0.19 | 0.42 | META - TG - CURDRINK |
| rs34311866 | 4:951947 | C/T | 0.83 | <i>TMEM175</i> | -0.0200 | 0.0040 | 1.5×10^{-11} | 2.1×10^{-6} | 0.42 | 0.90 | EUR - TG - CURDRINK |
| rs2911971 | 8:6607634 | G/C | 0.34 | <i>AGPAT5</i> | -0.7500 | 0.0100 | 7.5×10^{-11} | 1.1×10^{-5} | 0.53 | 0.49 | META - LDL-C - CURDRINK |
| rs56076449 | 5:132442190 | G/T | 0.79 | <i>HSPA4 / FSTL4</i> | 0.0130 | -0.0020 | 9.3×10^{-11} | 1.3×10^{-5} | 0.80 | 0.80 | META - TG - REGDRINK |
| rs41274050 ^e | 10:52573772 | T/C | 0.01 | <i>A1CF</i> | 0.1080 | -0.0310 | 9.6×10^{-10} | 1.3×10^{-4} | 0.62 | 1.00 | EUR - TG - REGDRINK |
| rs7035578 | 9:78745177 | A/G | 0.15 | <i>PCSK5</i> | -1.2700 | 0.0800 | 1.2×10^{-9} | 1.6×10^{-4} | 0.70 | 0.82 | EUR - LDL-C - CURDRINK |
| rs201445483 | 2:17890087 | I/D | 0.83 | <i>SMC6</i> | 1.4300 | 0.6800 | 4.7×10^{-9} | 6.0×10^{-4} | 0.17 | 0.46 | META - LDL-C - CURDRINK |
| rs72729610 | 4:154190965 | G/A | 0.86 | <i>TRIM2</i> | 0.0075 | -0.0036 | 5.6×10^{-9} | 7.2×10^{-4} | 0.08 | 0.26 | META - HDL-C - REGDRINK |
| rs143528679 | 4:124558378 | G/A | 0.10 | <i>SPRY1 / LINC01091</i> | -1.2000 | -5.6300 | 6.3×10^{-9} | 8.0×10^{-4} | 6.4×10^{-4} | 0.10 | AFR - LDL-C - CURDRINK |
| rs2111622 ^e | 2:53984823 | G/A | 0.77 | <i>ASB3 / GPR75-ASB3</i> | 0.0008 | -0.0072 | 7.9×10^{-9} | 9.9×10^{-4} | 0.01 | 0.12 | EUR - HDL-C - CURDRINK |
| rs13284665 | 9:131513370 | G/A | 0.88 | <i>ZER1</i> | 1.9900 | -0.8900 | 1.1×10^{-8} | 1.3×10^{-3} | 0.35 | 0.89 | EUR - LDL-C - CURDRINK |
| rs4898521 | 12:49755162 | A/T | 0.95 | <i>DNAJC22 / SPATS2</i> | 0.0179 | -0.0107 | 1.3×10^{-8} | 1.7×10^{-3} | 0.06 | 1.00 | EUR - HDL-C - REGDRINK |
| rs6063050 | 20:45604240 | C/T | 0.75 | <i>EYA2</i> | 0.0110 | 0.0000 | 2.9×10^{-8} | 3.6×10^{-3} | 0.30 | 0.39 | META - TG - CURDRINK |
| rs2963472 | 5:157999022 | A/G | 0.21 | <i>LOC101927697 / EBF1</i> | 0.0140 | -0.0020 | 3.5×10^{-8} | 4.2×10^{-3} | 0.96 | 0.23 | EUR - TG - REGDRINK |

rsID: Reference SNP ID. Chr: Chromosome number. Freq: Frequency of the coded allele. FDR: False discovery rate. DF: Degrees of freedom. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. TG: Triglycerides. AFR: African ancestry. EUR: European ancestry. META: trans-ancestry meta-analysis. CURDRINK: alcohol consumption categorized into drinkers

and non-drinkers. REGDRINK: alcohol consumption categorized into regular drinkers and not regular drinkers. ^aThe Alleles column reports the coded/non-coded alleles. ^bThese estimates pertain to the 2 DF joint test of main and interaction effects. ^cThese *P*-values pertain to 1 DF tests of interaction effects. ^dThe Heterogeneity *P*-value column indicates the significance of the Stage 1 heterogeneity across ancestry groups in the most significant 2 DF Model. ^eThese loci were also discovered by a concurrent association study focused on exonic variants (37).

ORIGINAL UNEDITED MANUSCRIPT

FIGURE LEGENDS

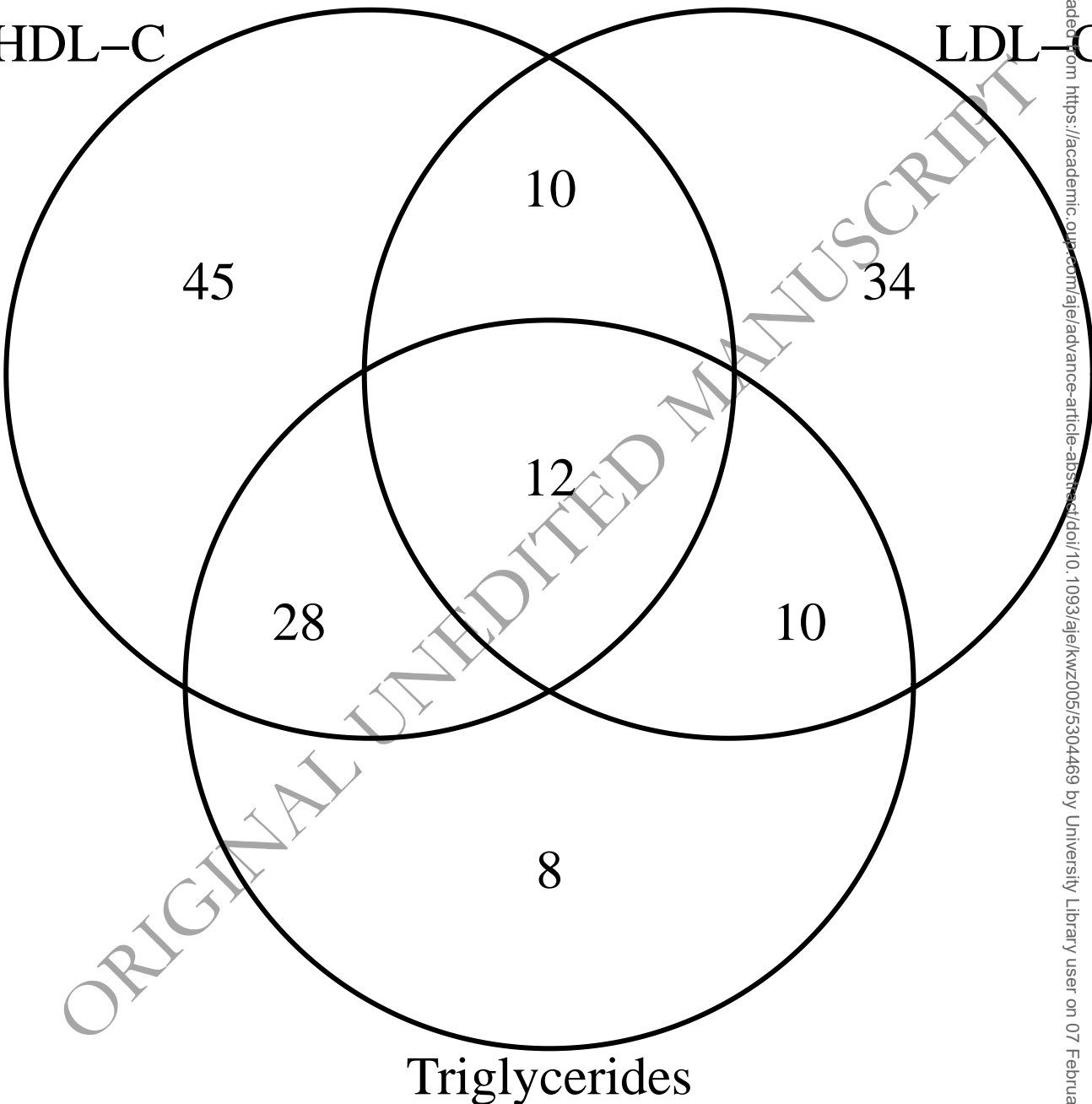
Figure 1. Venn Diagram Showing the Distribution of Genome-wide Significant Associations at the 147 Identified Loci Among Lipid Traits. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol.

Figure 2. Heat Map of the Significance and Effect Direction of Index Variants at the 18 Novel Loci for the Three Lipid Traits.

For each combination of index variant and lipid trait, the effect direction and *P*-value of the most significant association is shown. For example: the 11:63911273 variant was most significantly associated with high-density lipoprotein cholesterol in the trans-ancestry meta-analysis, using the current drinker alcohol consumption variable. Shades of purple and yellow represent negative and positive directions of effect, respectively, while associations of either direction with *P*-value > 0.05 are white. Effect +: the direction of effect is greater than or equal to zero. Effect -: the direction of effect is less than zero.

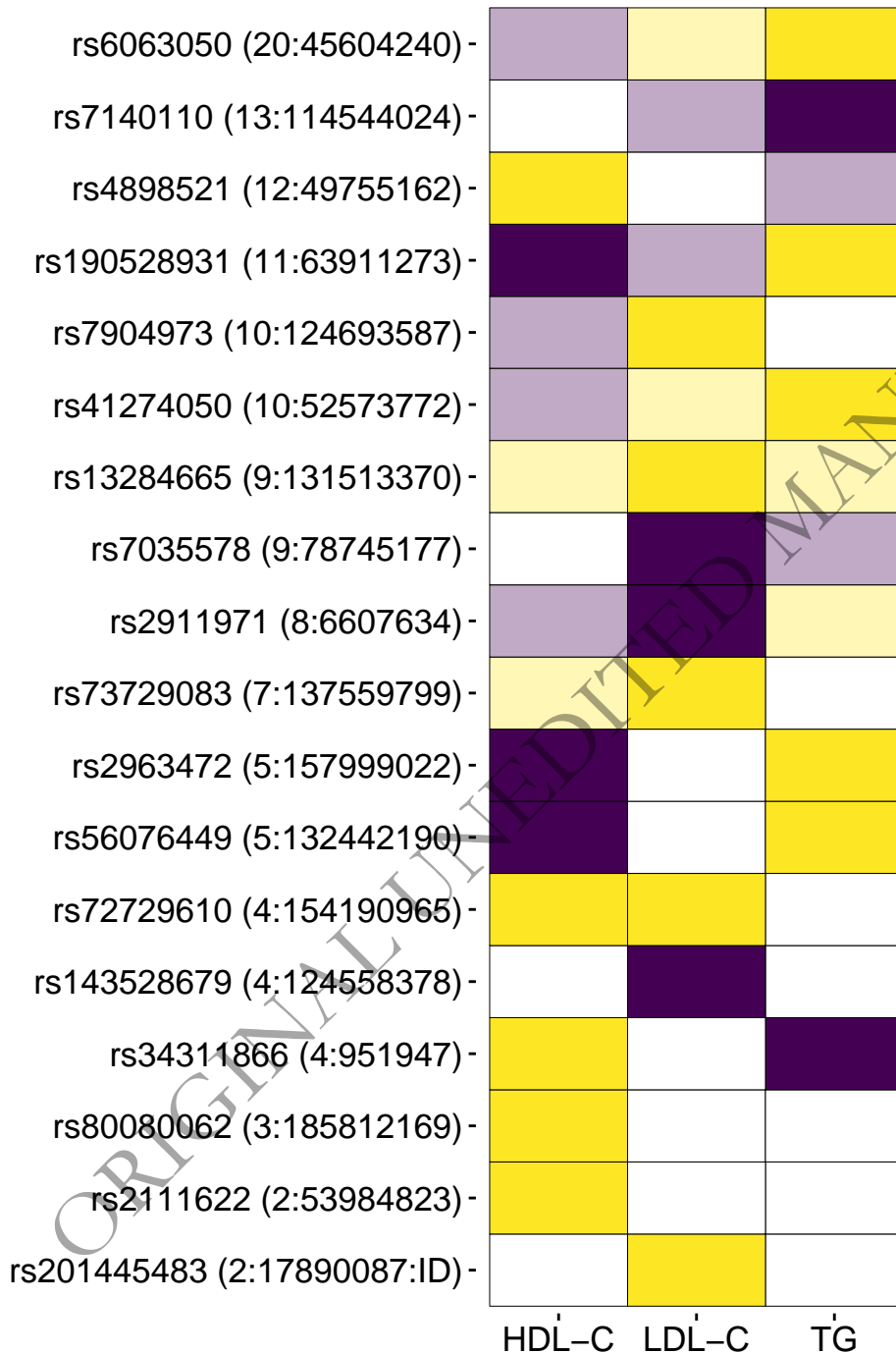
HDL-C

LDL-C



Triglycerides

ORIGINAL UNEDITED MANUSCRIPT



Joint 2-df *P* Value

